Fluid Resuscitation in Critically Ill Patients with Acute Kidney Injury (AKI)

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Prevalence of acute renal failure in Intensive Care Unit (ICU): Survey of 23 countries

- 29,269 admitted to ICU from September 2000 to December 2001 at 54 hospitals in 23 countries
- Median age – 67 (53 - 75 years)
- Sepsis (47.5%) – most common contributing factor
- 30% had preadmission renal failure
- 60.3% overall hospital mortality
- 13.8% dialysis dependent at hospital discharge

JAMA, August 17, 2005, 294:813-818
Percent of hospitalizations with AKI 2004 - by age, sex and race

Source: National Center for Health Statistics, National Hospital Discharge Survey
Age and frequency of AKI

36-70% of AKI occurs in individuals over 70 years (even though they constitute only 7% of the population)
Probability of hospitalization for AKI in patients with & without pre-existing CKD: 2002
Probability of ESRD following AKI in one year in patients with & without CKD: 1995 to 2003

- 1995: CKD 5.2%, No CKD 1.0%
- 1998: CKD 5.4%, No CKD 0.7%
- 2001: CKD 4.8%, No CKD 0.6%
- 2003: CKD 3.7%, No CKD 0.6%

Source: USRDS 2006 ADR
Effect of Extracellular Fluid (ECF) Excess in CKD on Left Ventricle Mass (LVM)

$R^2 = 0.23$, $p<0.0001$

Effect of ECF Excess in CKD on Left Ventricular Diastolic Dysfunction

\[ R^2 = 0.18 \text{ } p<0.0001 \]
Effect of ECF Excess in CKD on Intima Media Thickness (IMT) in Common Carotid Artery

$R^2 = 0.19, p < 0.0001$

Natural history of sepsis
Prospective study (n=2527)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>ARF (%)</th>
<th>ARDS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sepsis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 criteria</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>2 criteria</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>3 criteria</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td><strong>Severe sepsis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture (+)</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Culture (-)</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td><strong>Septic shock</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture (+)</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Culture (-)</td>
<td>38</td>
<td>18</td>
</tr>
</tbody>
</table>

Rangel-Frausto et al JAMA, 1995
Sepsis and Acute Kidney Injury (AKI)

Incidence of AKI with sepsis
(Rangel-Frusto et al, JAMA, 1995)

- Moderate sepsis – 19%
- Severe sepsis – 23%
- Septic shock – 51%
- 48% of AKI is related to sepsis

Mortality
(Brivet et al, Crit Care Med, 1996)

- Septic patient with AKI – 73%
- Non-septic patient with AKI – 45%
Sepsis and Acute Renal Failure

Renal Vasoconstriction with Sodium and Water Retention

- ↑ RAAS
- ↑ AVP
- ↑ Sympathetic Tone

Bacteria and Endotoxemia

- Induction of Nitric Oxide Synthase
- Nitric Oxide-mediated Arterial Vasodilation
- Arterial Underfilling and Baroreceptor Activation

Interstitial volume (IV) in control and minoxidil-treated rats

*Sanz et al.: J Cardiovasc Pharmacol 15:485-492, 1990*

* * P < 0.05 with respect to controls; ** P < 0.05 with respect to basal

Interstitial pressure (IP) in control and minoxidil-treated rats


* P<0.05 with respect to controls

Saline

Albumin

IP (mm Hg)

Time (min)
Mechanical Ventilation in AKI

- Sepsis and Endotoxemia
- Systemic Vasodilation and AKI
  - Excess Fluid Administration
  - Increased Albumin Distribution
  - Altered Starling Forces

- Increased Interstitial Volume
- Pulmonary Edema and Hypoxia
  - Mechanical Ventilation
  - Barotrauma
  - Infection
  - Oxygen Toxicity

- ARDS
- MODS

80-90% Mortality

351:159-69, 2004
Association between fluid accumulation and mortality in acute kidney injury

Effect of Fluid Overload on Mortality in 400 Critically Ill Children

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Survivors</th>
<th>Non-Survivors</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 (ref 1)</td>
<td>16%</td>
<td>34%</td>
<td>0.03</td>
</tr>
<tr>
<td>77 (ref 2)</td>
<td>&lt; 10%</td>
<td>&gt; 10%</td>
<td>0.002</td>
</tr>
<tr>
<td>113 (ref 3)</td>
<td>9%</td>
<td>16%</td>
<td>0.01</td>
</tr>
<tr>
<td>116 (ref 4)</td>
<td>14%</td>
<td>25%</td>
<td>0.002</td>
</tr>
<tr>
<td>76 (ref 5)</td>
<td>7%</td>
<td>22%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

References:
Septic ARF-prospective multicenter study.  
Patient Characteristics.  n=345

<table>
<thead>
<tr>
<th>ARF:</th>
<th>Septic ARF (%)</th>
<th>Non-septic ARF (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>52%</td>
<td>68%</td>
<td>0.01</td>
</tr>
<tr>
<td>During ICU stay</td>
<td>48%</td>
<td>32%</td>
<td>0.01</td>
</tr>
<tr>
<td>Oliguria</td>
<td>55%</td>
<td>50%</td>
<td>NS</td>
</tr>
<tr>
<td>sCreat (mg/dl)</td>
<td>4.3</td>
<td>5.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>47%</td>
<td>51%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mech. vent</strong></td>
<td><strong>70%</strong></td>
<td><strong>47%</strong></td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>APACHE II</td>
<td>29.6</td>
<td>24.3</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>10</td>
<td>9.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>74.5</td>
<td>45.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Neveu et al, NDT, 1996
### Independent risk factors for hospital mortality with AKI in ICU

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Vasopressors</td>
<td>1.95</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>2.11</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>1.36</td>
<td>&lt; .03</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>1.41</td>
<td>= .02</td>
</tr>
<tr>
<td>Hepatorenal Syndrome</td>
<td>1.87</td>
<td>= .03</td>
</tr>
</tbody>
</table>

JAMA, August 17, 2005, 294:813-818
Vasopressin in Septic Shock Trial (VASST)

**Inclusion**
- 779 patients in septic shock requiring vasopressors for at least 6 hours and
- One additional organ dysfunction for less than 24 hours.
- Randomized to norepinephrine (NE) or vasopressin (AVP)

**Primary Endpoint** – 28 day survival
- No difference

Vasopressin in Septic Shock Shock Trial (VASST) (cont.)

Stratification on enrollment by severity of Hypotension

- Greater or less than 15 μg/min of NE
- Patients receiving less than 15 μg/min of NE had improved 28 day survival (26.5 versus 35.7%, \( p = 0.05 \)) and 90 day survival (35.8 versus 46.1%, \( p = 0.04 \))
- No difference in BP but lower doses of NE with AVP group

Daily Cumulative Fluid Balance in Septic Shock

Effect of Fluid Balance at 12 hours on Survival in Septic Shock

Adjusted Survival Curves
Fluid Balance Quartiles 12 hours

Survival (adjusted for APACHE II, age, and dose NE)

Days

1st quartile – 710 ml
2nd quartile – 2880 ml
3rd quartile – 4900 ml
4th quartile – 8150 ml

Effect of Cumulative Fluid Balance at 4 days on Survival in Septic Shock

Adjusted Survival Curves
Fluid Balance Quartiles 4 days

1st quartile – 1560 ml
2nd quartile – 8120 ml
3rd quartile – 13,000 ml
4th quartile – 20,500 ml

Survival (adjusted for APACHE II, age, and dose NE)

Days

Fluid balance on study enrollment (12 hrs) significantly correlates with central venous pressure (A) and dose of norepinephrine (B)

A

CVP (mmHg)

Fluid Balance on Enrollment (mL)

R = 0.20

B

Dose of Norepinephrine (μg/min)

Fluid Balance on Enrollment (mL)

R = 0.25

Day 4 fluid balance during the preceding 24 hrs does not correlate with central venous pressure (A) nor with the dose of norepinephrine (B).

## Beneficial effects of early goal-directed therapy of severe sepsis and septic shock (7-72hr)

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Early goal</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality (%)</td>
<td>46.5</td>
<td>30.5</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>SCVO$_2$ (%)</td>
<td>65.3</td>
<td>70.4</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.9</td>
<td>3.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>pH</td>
<td>7.36</td>
<td>7.4</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td>16.8</td>
<td>2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrin split product (µg/dl)</td>
<td>62</td>
<td>39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Rivers et al, NEJM, 2001
SAFE Study - Survival comparison between patients assigned to receive albumin and those assigned to receive saline

Comparison of Saline and Albumin in 603 Patients with Severe Sepsis

<table>
<thead>
<tr>
<th></th>
<th>28 day Death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (N=185)</td>
<td>30.7%</td>
<td></td>
</tr>
<tr>
<td>Saline (N=217)</td>
<td>35.3%</td>
<td></td>
</tr>
<tr>
<td>Relative Risk</td>
<td>.87 (CI 0.74 to 1.02)</td>
<td>P = 0.09</td>
</tr>
</tbody>
</table>

FLUID OVERLOAD
Comparison of two fluid-management strategies in acute lung injury
Fluid and Catheter Treatment Trial (FACTT)

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network
Protocol

- Randomized to compare conservative to liberal strategy of fluid management for 7 days in 1000 patients with acute lung injury

- Primary endpoint – death at 60 days

- Secondary endpoints
  - Number of ventilator-free days
  - Organ-failure-free days
  - Measures of lung physiology

Frequency of furosemide and fluid bolus therapies in liberal versus conservative groups

Comparison of cumulative fluid balance at day 7 from baseline between liberal and conservative groups who were shock-free (left) and shock-present (right)

Comparison of cumulative fluid balance in liberal versus conservative groups and previous ARDS network studies (ARMA and ALVEOLI)

Stable CVP in liberal fluid group as CVP declines in conservative fluid group

Results

- Mean cumulative fluid balance was significantly different (-136 49/ml vs 6992 502 ml, p <0.001)
- Rate of death at 60 days between the conservative and liberal fluid management strategies was no different (25.5% vs. 28.4%, p = 0.30)
- No increase in use of dialysis during first 60 days (10% vs 14%, p = 0.06)
- Renal failure (serum creatinine of at least 2 mg/dl), 5.5 versus 5.5 organ failure-free days (NS) from days 1-7.

Results

Conservative approach improved:

- Oxygenation
- Lung injury score
- Ventilator-free days (14.6 ± 0.5 vs 11.2 ± 0.4 days, p < 0.001)
- Days not spent in ICU during first 28 days (13.4 ± 0.4 vs 11.2 ± 0.4, p <0.001)

“These results support the use of a conservative strategy of fluid management in patients with acute lung injury.”
Fluid Balance, Diuretic Use and Mortality in Acute Kidney Injury (AKI)
NHLBI Acute Respiratory Distress Syndrome Network

Data source – Fluid and Catheter Treatment Trial (FACTT) randomized controlled multicenter trial of 1400 patients with acute lung injury

Purpose – Evaluate post-renal injury fluid balance and diuretic use with 60 day mortality of patients who developed AKI (defined as AKIN stage 1 or greater)

Results – 306 patients developed AKI in first 2 study days (137 in fluid liberal and 169 in fluid conservative (p=0.04 )

Post-AKI fluid balance associated with increased AKI mortality (OR 1.61, p<0.001)

Higher post-AKI furosemide doses decreased AKI mortality (OR 0.48, p – 0.007) but this was not significant after adjusting for fluid balance

Conclusion – positive fluid balance after AKI strongly associated with increased 60 day mortality; protective effect of high furosemide likely due to effect on fluid balance

Effect of Fluid Overload on Heart Function in AKI

Excess fluid administration in AKI

↑ ECF volume

↑ Cardiac filling pressure

Impaired cardiac function

Mitral insufficiency

Ventricular wall stress and endomyocardial ischemia

↑ Cardiac dilatation

Benefits of Excess Fluid Removal in AKI

Excess ECF

Ultrafiltration Treatment

- Negative Sodium and Water Balance
- Decreased Cardiac Filling Pressure
- Decreased Ventricular Dilatation
- Decreased Ventricular Wall Stress and Endomyocardial Ischemia
- Decreased Functional Mitral Insufficiency
- Improved Myocardial Function
- Improved Renal Function

Improved Pulmonary Congestion

Effect of Fluid Overload on Kidney Function in AKI

Excess extracellular fluid
- Increased renal venous pressure
- Increased tubule and interstitial pressures
- Stimulation of RAAS and SNS
- Decreased glomerular filtrate rate and renal blood flow
